

REMARKS

Claims 8-10 have been canceled. Claims 1, 7, 14, 16-17 have been amended to more precisely define the invention, and claims 19-21, drawn to preferred features of claims 7, 16 and 17, respectively, have been added.

The claims are now 1-7 and 11-21.

Prior claim 8 was rejected under 35 U.S.C. 112, first paragraph, as not adequately enabled; claims 7, 9, 14, 16 and 17 under 35 U.S.C. 112, second paragraph, as being indefinite; and claims 1-18 under 35 U.S.C. 103(a) as being unpatentable under Latorse (WO 96/03044), Shibata et al. (EP 0775 696 A1) and Seitz et al. (EP 0472 996 A1)), in view of Budavari (Merck Index, 11th ed., 1989, monograph 4964).

The present Amendment obviates the rejections under 35 U.S.C. 112, first and second paragraphs.

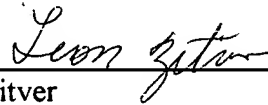
The rejection under 35 U.S.C. 103(a) is respectfully traversed.

While not explicitly stated, it appears that the four references applied by the Examiner are intended to be used in combination. However, no combination of these references suggests the synergistic effect of the presently claimed composition, attention being directed to the fact that the claims are specifically directed to synergistic compositions.

Submitted herewith is a copy of a report by M.P. Latorse and B. Givois, evidencing the synergistic relationship between fencaramide and fosetyl. Proper attestation of this report will be provided. While the report deals with a combination of specific compounds, one skilled in the art would realize that it is indicative of synergism of the genera which the compounds represent.

For the reasons above presented, allowance of this application is respectfully solicited.

Respectfully submitted,



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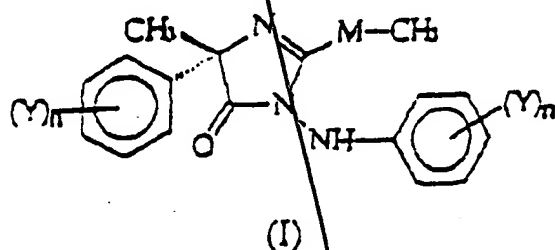
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LZ/cpf
Enclosure

APPENDIX A
"CLEAN" VERSION OF EACH PARAGRAPH/SECTION/CLAIM
 37 C.F.R. § 1.121(b)(ii) AND (c)(i)

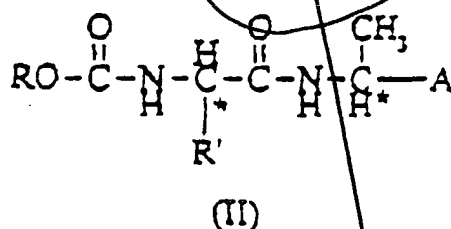
CLAIMS (with indication of amended or new):

1. (Amended) A synergistic fungicidal composition comprising a compound (1) of
 formula:



in which:

- M represents an oxygen or sulfur atom;
 - n is an integer equal to 0 or 1;
 - Y is a fluorine or chlorine atom or a methyl radical;
- and a compound of formula (II):

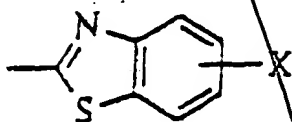


in which:

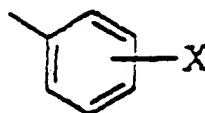
- R and R', which are identical or different, are chosen, independently of each other, from a linear or branched alkyl radical containing from 1 to 6 carbon atoms,

25 - A represents a group chosen from A1 and A2 which have the respective formulas:

B 2



(A1)



(A2)

and

30 - X represents a hydrogen atom, a halogen atom chosen from chlorine, fluorine, bromine and iodine, a linear or branched alkyl radical containing from 1 to 6 carbon atoms, or a linear or branched alkoxy radical containing from 1 to 6 carbon atoms, and

- the asterisks represent asymmetric centers;

35 the compound (I)/compound (II) ratio being between 5 and 0.5.

B 2
Sub C1
7. (Amended) The fungicidal composition as claimed in claim 1, characterized in that it comprises, in addition, another fungicidal active material.

B 3
Sub C2
contd
14. (Amended) A process for curatively or preventively controlling the phytopathogenic fungi of crops of the phytophthora and plasmopara genera characterized in that an effective and non-phytotoxic amount of a fungicidal composition as claimed in claim 1 is applied onto the vegetation to be treated.

B 4
16. (Amended) The process as claimed in claim 14, characterized in that the amount of fungicidal composition corresponds to a dose of compound (I) of between 10 and 500 g/ha.

17. (Amended) The process as claimed in claim 14, characterized in that the amount of fungicidal composition corresponds to a dose of compound (II) of between 10 and 500 g/ha.

B 5
19. (New) The fungicidal composition as claimed in claim 7, wherein said another fungicidal active material is iprodione.

cont
B5

20. (New) The process as claimed in claim 16, wherein the amount of the fungicidal composition corresponds to a dose of compound (I) of between 20 and 300 g/ha.

21. (New) The process as claimed in claim 17, wherein the amount of fungicidal composition compound to a dose of compound (II) of between 20 and 300 g/ha.

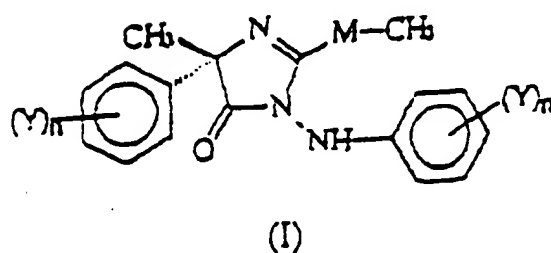
APPENDIX B

VERSION WITH MARKINGS TO SHOW CHANGES MADE

37 C.F.R. § 1.121(b)(iii) AND (c)(ii)

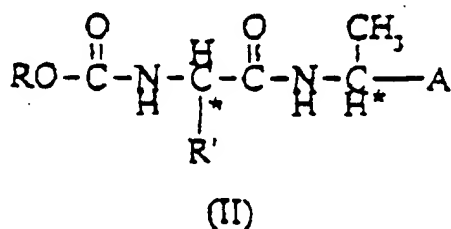
CLAIMS:

1. (Amended) A synergistic fungicidal composition comprising a compound (1) of formula:



10 in which:

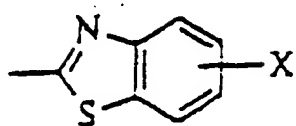
- M represents an oxygen or sulfur atom;
 - n is an integer equal to 0 or 1;
 - Y is a fluorine or chlorine atom or a methyl radical;
- and a compound of formula (II):



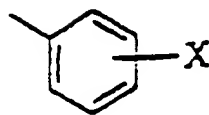
20 in which:

- R and R', which are identical or different, are chosen, independently of each other, from a linear or branched alkyl radical containing from 1 to 6 carbon atoms,

25 - A represents a group chosen from A1 and A2 which have the respective formulas:



(A1)



(A2)

and

30 - X represents a hydrogen atom, a halogen atom chosen from chlorine, fluorine, bromine and iodine, a linear or branched alkyl radical containing from 1 to 6 carbon atoms, or a linear or branched alkoxy radical containing from 1 to 6 carbon atoms, and

- the asterisks represent asymmetric centers;

35 the compound (I)/compound (II) ratio being [between 50 and 0.01, preferably between 10 and 0.01 and even more preferably] between 5 and 0.5.

7. (Amended) The fungicidal composition as claimed in claim 1, characterized in that it comprises, in addition, another fungicidal active material[, in particular iprodione].

14. (Amended) A process for curatively or preventively controlling the phytopathogenic fungi of crops of the phytophthora and plasmopara genera characterized in that an effective and non-phytotoxic amount of a fungicidal composition as claimed in claim 1 is applied onto the vegetation to be treated.

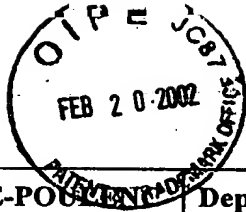
16. (Amended) The process as claimed in claim 14, characterized in that the amount of fungicidal composition corresponds to a dose of compound (I) of between 10 and 500 g/ha [preferably between 20 and 300 g/ha].

17. (Amended) The process as claimed in claim 14, characterized in that the amount of fungicidal composition corresponds to a dose of compound (II) of between 10 and 500 g/ha [preferably between 20 and 300 g/ha].

19. (New) The fungicidal composition as claimed in claim 7, wherein said another fungicidal active material is iprodione.

20. (New) The process as claimed in claim 16, wherein the amount of the fungicidal composition corresponds to a dose of compound (I) of between 20 and 300 g/ha.

21. (New) The process as claimed in claim 17, wherein the amount of fungicidal composition compound to a dose of compound (II) of between 20 and 300 g/ha.



RHONE-POULICEN SECTOR AGRO	Department:	Chrono N .:	DOC No. : 441641
	R&D/CRLD/FONG	9730183	Date: 29/05/97
	GOoD Study No.: 10111		
External Organism(s):			

Author(s): M.P. LATORSE, B. GIVOIS

Internal:

External:

Title: Study in vivo on *Plasmopara viticola* (vine downy mildew) in the case of a 24 h curative treatment and an antisporeulating treatment (D + 5 days) of the ternary combination of RPA407213 with the fosetyl AL mixture combined with fencaramide (Bay 12920F)

Key words:

RPA407213, Bay 12920F fencaramide, fosetyl AL, curative synergy, vine downy mildew

Summary & conclusions:

A particularly promising synergy was demonstrated between the three products RPA407213, fencaramide and fosetyl Al applied in a ternary mixture against vine downy mildew in the case of a 24 h curative treatment and an antisporeulating curative treatment (+ 5 days). The advantageous ratios cover the following values:

$$\begin{aligned} \text{RPA407213}/(\text{fencaramide} + \text{fosetyl}) &= 1/(1 + 10), \\ \text{and RPA407213}/(\text{fencaramide} + \text{fosetyl}) &= 2/(1 + 10) \end{aligned}$$

M.P. LATORSE

[signature]

Study in vivo on *Plasmopara viticola* (vine downy mildew) in the case of a 24 h curative treatment and an antispurulating treatment (D + 5 days) of the ternary combination of RPA407213 with the fosetyl AL mixture combined with fencaramide (Bay 12920F)

Objective: To demonstrate a synergy between these three products on vine downy mildew, knowing that Bayer is actively working on the combination of fencaramide with fosetyl in a dose ratio corresponding to the ratio 0.092 (120 g/ha Bay12920F/1 300 g/ha fosetyl) and that our relationship with Bayer is strategic for the development of RPA407213.

Materials and methods:

Taking into account the studies initiated by Bayer on the combination Bay12920F and fosetyl AL in the treatment of vine downy mildew, we chose to consider in this first study a binary mixture in the fixed ratio Bay12920F/fosetyl = 1/10 to be combined with RPA407213 (product A).

It should be recalled that the binary combination RPA407213/Bay12920F studies solely in the context of a preventive application against vine downy mildew and potato blight did not make it possible to demonstrate a synergy under these conditions. The main reasons which led us to work primarily with the ternary mixture in order to demonstrate a possible synergy as a curative or antispurulating application are on the one hand that neither fencaramide alone, nor RPA407213 alone are potentially highly curative products in the case of WG formulations under development on vine downy mildew and, on the other hand, that the RPA407213 X fosetyl combination has shown an advantageous curative or even antispurulating potential in the field.

Products:

RPA product No.	Formulations	EXP	OP
A: RPA407213	WG 700	10625A	950624
B: RPA530126 (Bay12920F)	WG 500	10705A	050634
C: fosetyl	WG 800	(V 70312520)	Allette Industriel

A suspension for spraying of the two products Bay12920F and fosetyl in a fixed ratio of 1/10 (close to 120/1 300) was prepared from the above granular formulations and the A(RPA407213)/(B(BAY12920F) + C(fosetyl)) ratio was varied. The ratios studied were chosen between A/(B + fosetyl) between 0.125/(1 + 10) and 2/(1 + 10).

Vine cuttings (*Vitis vinifera*), Chardonnay variety, are cultivated in pots. When these plants are 2 months old (8- to 10-leaf stage, height 10 to 15 cm), they are treated by spraying using a treatment tower provided with cross-jet nozzles delivering of the order of 1 000 l per ha of volume of plant protection mixture for covering of the top and bottom sides of the leaves.

Plants used as controls are treated with water containing no active ingredient.

In the case of curative or antisporeulating treatments, the plants are infected prior to the fungicidal treatment by spraying an aqueous suspension of *Plasmopara viticola* sporocysts obtained from sporulated leaves infected 7 days earlier. These spores are suspended at the rate of 100 000 units per cm³.

The infected plants are then incubated at 18-20°C under 90-100% relative humidity for 24 h. The treatment is carried out, in the case of a 24 h curative application, after the plants have been left to dry for 1 h at 70% RH at 20°C.

In the case of an antisporeulating application, the plants are also maintained at 70% RH at 20°C for 4 days before the treatment takes place.

In both cases, after the fungicidal treatment, and in order to avoid washing out the treatment product, the plants are maintained for 1 h in an atmosphere with 70% RH before being again placed in incubation cases at 90-100% RH in order to facilitate the development of the mildew.

The reading of the rates of infection, expressed by estimating the sporulated bottom surface area of the leaves, is carried out 7 days after the infection, in comparison with the control plants.

The results obtained are presented in the form of points, corresponding to 50, 70 or 90% destruction of the parasite and placed in a TAMMES isobole diagram which comprises on the x-axis the doses of A (RPA407213) expressed in mg/l and on the y-axis the doses of B (Bay12920F) also in mg/l knowing that fosetyl (C) is always present in the mixture in the B/C ratio of 1/10 relative to product B.

Results:

We chose to present in two tables the numerical results corresponding to the ED50, 70 and 90% values (effective doses providing 50, 70 or 90% control of the disease) for the different ratios of the mixtures studied, calculated on the basis of 3 repeats per factor. Also presented in these tables are the limits of the confidence interval in which these ED values exist for a 95% risk.

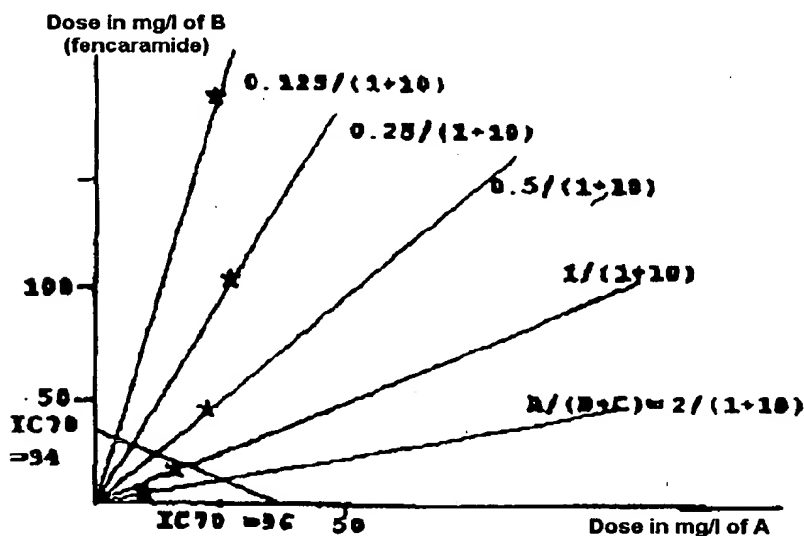
The illustration in the form of a TAMMES representation is only given for the ED70 values, the phenomenon observed being the same for the ED50 and 90 values.

1) 24 h curative application on vine downy mildew

Table 1: 24 h curative application on vine downy mildew
Fosetyl (C) is inactive alone at all the doses studied ($ED_{70} > 2\ 400\text{ mg/l}$)

	ED50 (confidence inc.)	ED70 (confidence inc.)	ED90 (confidence inc.)
A = RPA407213	20 (15-28)	36 (25-52)	88 (49-157)
B = Bay12920F	22 (15-32)	34 (22-53)	69 (34-139)
$A/(B+C) = 0.125/(1+10)$	14 (10-20)	24 (16-35)	55 (31-98)
$A/(B+C) = 0.25/(1+10)$	15 (10-22)	25 (16-39)	55 (28-106)
$A/(B+C) = 0.5/(1+10)$	10.7 (7-16)	21 (13-33)	58 (27-124)
$A/(B+C) = 1/(1+10)$	9.9 (6.5-15)	17 (10-27)	38 (19-77)
$A/(B+C) = 2/(1+10)$	5.8 (3.8-8.1)	9 (6-13.6)	20 (11-37)

TAMMES representation of the ED70 values (= IC70 inhibitory concentration)

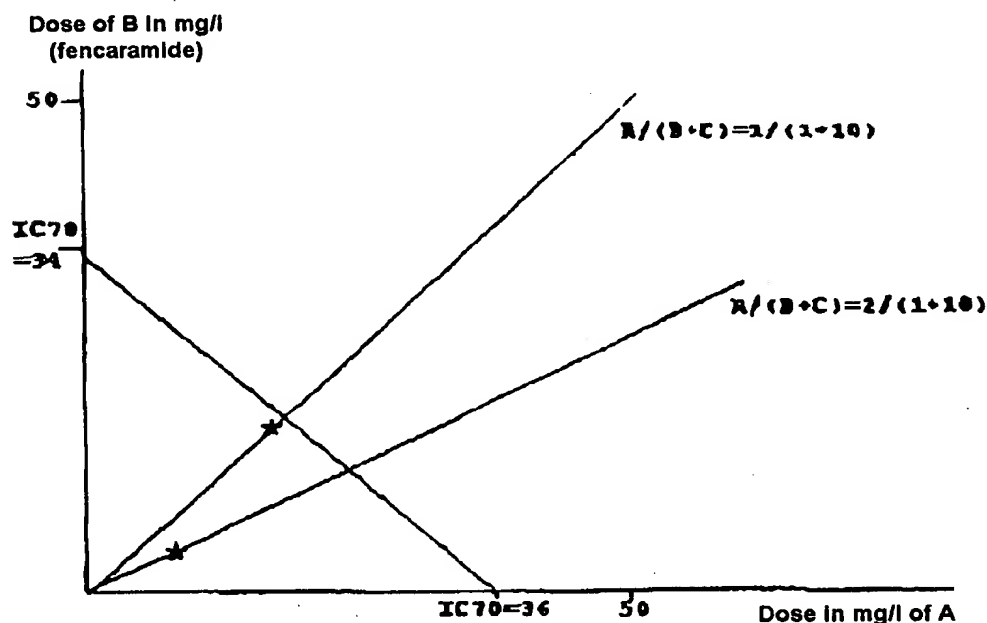


The arrangement of the points obtained indicates a two-sided effect according to the TAMMES method. This arrangement corresponds to a type III isobole according to said method (TAMMES P.M.L. (1964) *Isoboles, a graphic representation of synergism in pesticides*; *Netherlands Journal of Plant Pathology* 70, 73-80).

The arrangement of the points corresponding to the $A/(B+C)$ ratios equal to $0.125/(1+10)$ and $0.25/(1+10)$ means that the products are potentially in a situation of antagonism. In the case of the $0.5/(1+10)$ ratio, there is loss of additivity of the ternary mixture relative to the products alone whereas for the $1/(1+10)$ ratio an additive situation is observed.

When fencaramide is at a lower dose by a factor of 2 in the mixture than that of RPA407213, the synergy which is demonstrated is then significant (cf. Table 1).

The two situations of additivity and synergy appear in the enlarged graph below. The relevant ratios RPA407213/(Bay12920F + fosetyl) equal to $1/(1+10)$ and $2/(1+10)$ correspond to agronomically very advantageous ratios in favor of RPA407213 relative to fencaramide.



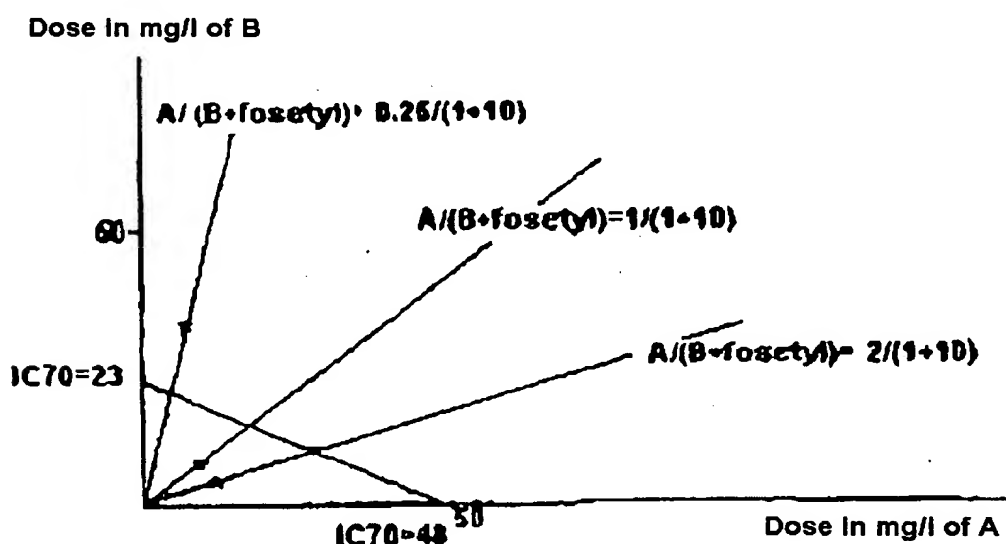
It appears significantly that when the mixture (fencaramide X fosetyl) in the 1/10 ratio is added to RPA407213, the dose of RPA407213 necessary for controlling the mildew during a 24 h curative treatment for the $2/(1+10)$ ratio is decreased below 36 mg/l which corresponds to the only dose of RPA407213 which it is necessary to apply in order to obtain a percentage control of 70% of the disease.

2) Antisporulating application (treatment 5 days after the infection) on vine downy mildew

Table 2: Antisporulating curative application 5 days after infection on vine downy mildew
Fosetyl (C) is inactive alone at all the doses studied ($ED_{70} > 2\ 400$ mg/l)

	ED50 (confidence inc.)	ED70 (confidenc inc.)	ED90 (confidence inc.)
A = RPA407213	24 (15-38)	48 (28-82)	146 (62-347)
B = Bay12920F	12.8 (6.8-24)	23 (12-46)	60 (21-169)
$A/(B+C) = 0.25/(1+10)$	12.1 (9.2-15.8)	19 (14-25)	38 (25-59)
$A/(B+C) = 1/(1+10)$	6.5 (4.7-8.9)	9.1 (6.4-12.9)	16 (9-26)
$A/(B+C) = 2/(1+10)$	5.6 (3.7-8.5)	10.3 (6.7-15.8)	27 (13-55)

TAMMES representation of the ED70 values (= IC70 inhibitory concentration)



It appears that when the binary mixture fencaramide X fosetyl in the 1/10 ratio is added to RPA407213, the dose of RPA407213 necessary for controlling the mildew is decreased below 48 mg/l which corresponds to the dose of RPA407213 alone which it is necessary to apply in order to obtain a percentage control of 70% of the disease and the dose of fencaramide is also decreased below 23 mg/l which corresponds to the dose of fencaramide alone which it is necessary to apply in order to obtain a percentage control of 70% of the disease, this being for the following two ratios: RPA407213/(fencaramide + fosetyl) equal to $1/(1+10)$ and to $2/(1+10)$.

The arrangement of the points on the TAMMES representation is characteristic for these two ratios of a synergy which may be considered as a significance limit (cf. Table 2).

Conclusion:

A particularly promising synergy was demonstrated between the three products RPA407213, fencaramide and fosetyl Al applied in a ternary mixture against vine downy mildew in the case of a 24 h curative treatment and an antispore-producing curative treatment (+ 5 days). The advantageous ratios cover the following values:

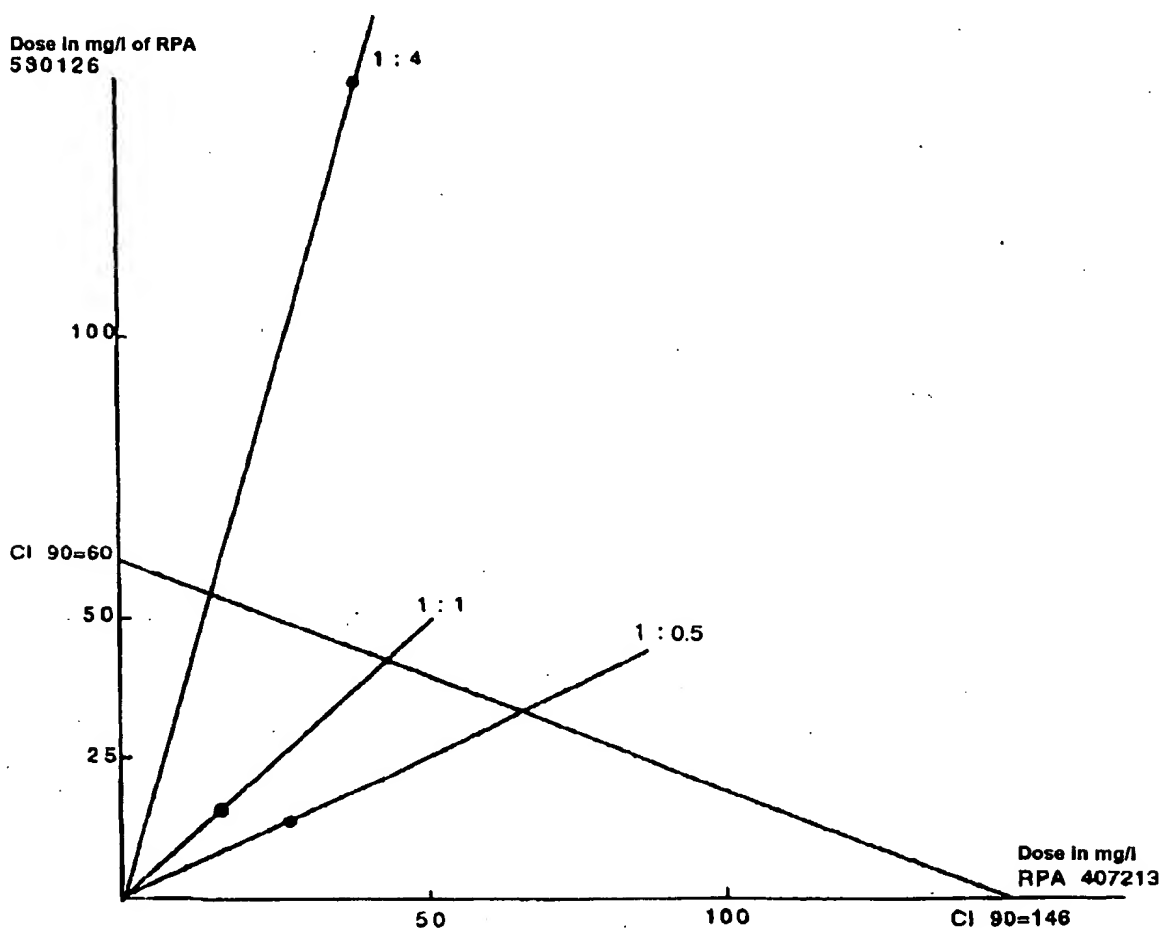
$$\begin{aligned} \text{RPA407213}/(\text{fencaramide} + \text{fosetyl}) &= 1/(1 + 10), \\ \text{and RPA407213}/(\text{fencaramide} + \text{fosetyl}) &= 2/(1 + 10) \end{aligned}$$

STUDY of SYNERGY RPA407213 combined with RPA530126 in the presence of
FOSETYL in the 530126/FOSETYL ratio 1/10
CURATIVE foliar treatment 5d on VINE Plants

Plasmopara Viticola

Study of SYNERGY according to TAMMES

Trial 030497



A SYNERGY exists at the 1:1 and 1:0.5 ratios of RPA407213:RPA5301326 and therefore 1:10 and 1:5 of RPA407213:fosetyl.